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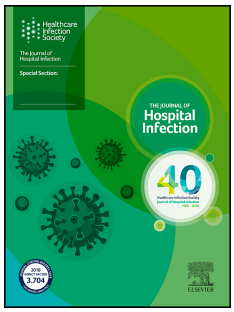


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# SARS-CoV-2 transmission risk upon return to work in RNA-positive healthcare workers

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## SUMMARY

### Background

Healthcare workers (HCWs) are at risk for coronavirus disease 2019 (COVID-19) and for spreading Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) amongst colleagues and patients.

### Aim

We aimed to study presence of SARS-CoV-2 RNA and possible onward transmission by HCWs upon return to work after COVID-19, and association with disease severity and development of antibodies over time.

### Methods

Unvaccinated HCWs with positive SARS-CoV-2 RT-PCR were prospectively recruited. Data on symptoms was collected via telephone questionnaires on day 2, 7, 14 and 21 after positive test. Upon return to work, repeat SARS-CoV-2 RT-PCR was performed and serum was collected. Repeat sera were collected at week 4, 8, 12 and 16 to determine antibody dynamics over time. Phylogenetic analysis was conducted to investigate possible transmission events originating from HCW with a positive repeat RT-PCR.

### Findings

Sixty-one (84.7%) participants with mild-moderate COVID-19 had a repeat SARS-CoV-2 PCR performed upon return to work (median 13 days post symptom onset), of which 30 (49.1%) were positive with a median cycle threshold (Ct) value of 29.2 (IQR 3.0). All HCWs developed antibodies against SARS-CoV-2. No significant differences in symptomatology and presence of antibodies were found between repeat RT-PCR-positive and -negative HCWs. Eleven direct colleagues of six participants with a repeat RT-PCR Ct-value <30 tested positive after the HCW returned to work. Phylogenetic and epidemiologic analysis did not

indicate onward transmission through HCW who were SARS-CoV-2 RNA positive upon return to work.

**Conclusions**

HCWs regularly return to work with substantial SARS-CoV-2 RNA loads. However, we found no evidence for subsequent in-hospital transmission.

**Key words:** SARS-CoV-2; COVID-19; Healthcare worker; Infectious disease transmission

## INTRODUCTION

Healthcare workers (HCWs) play a critical role in the response against the ongoing coronavirus disease 2019 (COVID-19) pandemic. Multiple studies show higher infection rates in HCWs compared to the general population, suggesting an occupational risk.[1-3] As for all confirmed cases, COVID-19 in HCWs requires measures to prevent transmission including quarantine. Hereby, (long) periods of absence can increase the strain on the healthcare system.

During this study, hospital guidelines prescribed that HCWs with confirmed COVID-19 could return to work 24 hours post symptom resolution. National and international guidelines generally recommend a minimal duration of isolation of 7 to 10 days after onset of COVID-19 symptoms and 24 hours to 5 days after improvement or resolution of symptoms.[4-7] Some guidelines mention the option of re-testing before returning to work for specific occasions (e.g., for HCWs with severe immune deficiencies),[5, 6, 8] but standard re-testing before returning to work is not recommended by any of the other guidelines since the assumed risk of transmission is considered negligible after these time periods.[9, 10]

On the other hand, Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) RNA can be detected in upper respiratory tract samples for prolonged periods, even without symptoms.[11] These cases are considered not to be infectious, as studies in mild cases of COVID-19 have found that no viable virus could be detected in individuals with prolonged shedding of SARS-CoV-2 RNA.[12, 13] However, in these studies samples were collected from 14 up to 30 days after diagnosis, whereas most HCWs may resume work sooner. In addition, in these studies viral culture was performed to determine infectivity and corresponding transmission risk. Since the standard procedure for HCWs returning to work in Dutch hospitals after a SARS-CoV-2 infection does not include RT-PCR or viral culture, viral loads at that time are not determined and the risk of transmission by mild cases who may return to work sooner remains unclear.

Repeat RT-PCR testing could further examine the risk of transmission of HCWs upon return to work. Furthermore, the presence of SARS-CoV-2 specific antibodies has been negatively correlated with the presence of infectious virus.[14, 15] Therefore, antibody dynamics could be valuable in determining the risk of transmission upon return to work and subsequent re-infection in this population with an increased occupational risk.

The aim of this prospective observational study is to assess the presence of SARS-CoV-2 RNA and corresponding cycle threshold (Ct) values upon resolution of symptoms in SARS-CoV-2 infected HCWs and its relation to disease severity, antibody dynamics and the risk of transmission.

## METHODS

### Study design

*Participants*

The Amsterdam University Medical Centres (Amsterdam UMC), the Netherlands, offers SARS-CoV-2 RT-PCR testing of combined nasopharyngeal and oropharyngeal swab specimens for HCWs with COVID-19-like symptoms (coughing, pharyngitis, dyspnoea, rhinitis and anosmia or dysgeusia). HCWs that tested positive in routine testing between May and September 2020, during the national 'second wave' and before the national vaccination campaign started, were invited to participate in this prospective observational study.

*Sampling process*

At day 2 after the positive SARS-CoV-2 RT-PCR, a telephone questionnaire regarding signs and symptoms at the time of disease onset as well as at the present time was administered. Hereby the presence of 14 predefined symptoms (coughing, pharyngitis, dyspnoea, rhinitis, abdominal pain, diarrhoea, nausea, vomiting, anorexia, fever, myalgia, headache, fatigue and

anosmia or dysgeusia) was determined. Follow-up symptomatology questionnaires were conducted at day 7, 14 and 21, as long as participants reported to experience symptoms.

Repeat nasopharyngeal and oropharyngeal swabs and initial serum were collected when HCWs returned to work. Hospital guidelines for returning to work required that all respiratory symptoms had to be resolved > 24 hours. Anosmia, dysgeusia and fatigue were not required to be resolved upon return to work. Repeat sera were collected at week 4, 8, 12 and 16 after the initial positive RT-PCR. All sera were stored at -20$^{o}$C until serological tests were performed.

The nasopharyngeal and oropharyngeal swabs were collected in E-swab or UTM viral transport medium (COPAN Diagnostics, Murrieta, CA, USA).

*Laboratory assays*

SARS-CoV-2 RNA was extracted using the MagNA Pure 96 system (Roche, Penzberg, Germany). RT-PCR targeting the SARS-CoV-2 E gene was performed according to a previously published protocol.[16] The presence of antibodies was determined by the ELISA-based Wantai SARS-CoV-2 double antigen sandwich total antibody assay (Wantai Biological Pharmacy, Beijing, China).

*Contact tracing in HCW that returned to work*

Standard contact tracing was performed for every SARS-CoV-2 positive HCW (or patient) by the Infection Control department. To investigate the transmission risk of HCWs with a positive repeat PCR, potential secondary infections were identified using data of the Occupational Health and Infection Control department. Potential secondary infections were defined as contacts within the same department that tested positive for SARS-CoV-2 within 7 days after study participants with a repeat RT-PCR Ct-value <30 returned to work.

Viral genomes of specimens of study participants and return-to-work contacts were amplified using the Ion AmpliSeq™ SARS-CoV-2 Research Panel and sequenced on an Ion GeneStudio S5 system (both from ThermoFisher Scientific, The Netherlands). Sequences were phylogenetically analysed to infer relatedness in a background of contemporaneous SARS-CoV-2 viral genomes from the Netherlands, derived from the GISAID database (Table SI). A maximum-likelihood phylogeny was constructed using the Augur pipeline.[17] We used procedures taken from [github.com/nextstrain/ncov] including the clock rate, reference genome, and site masking. Trees were visualised using ggtree[18] as implemented in R (R Core Team, Vienna, Austria).

**Ethics and Consent**

Informed consent was obtained from all participants. The study was reviewed and approved by the Amsterdam UMC institutional review board and conducted in accordance with the Declaration of Helsinki, and national and institutional standards.

**Statistical Analysis**

Unknown or missing answers in the symptomatology questionnaires were considered as absent. Fatigue and anosmia/dysgeusia were not included to determine disease duration. Sera with an absorbance/cut off ratio (s/c) above 1.1 were considered positive, samples with an s/c below 0.9 were considered negative. A s/c between 0.9 and 1.1 was considered indeterminate.

The data was analysed using RStudio (R Core Team, Vienna, Austria) and Graphpad Prism version 9.0.2 for Mac (GraphPad Software, San Diego, California USA). Normality checks were performed using the Shapiro-Wilk test. Descriptive analyses were made on baseline characteristics and the number of observations, presented as numbers and percentages. For

descriptive statistics, quantitative variables that did not follow a normal distribution were presented with median and interquartile range (IQR). Binomial logistic regression was used to calculate odds ratios and 95% CI for evaluating the association of the presence of symptoms with seroprevalence and presence of viral RNA. P values <0.05 were considered significant.

## RESULTS

### *Participants*

A total of 72 HCWs were included in this study. Demographics are shown in Table I. One HCW was admitted to the hospital (1.4%). Upon study inclusion, 20.8% of the HCWs reported to have worked while having COVID-like symptoms before they tested positive. Experiencing mild symptoms that were not directly recognized was the most common explanation.

### *Symptomatology*

The median time between disease onset and time of initial RT-PCR was 1 day (range 1-7). The median duration of symptoms was 10 days (range 0-41). Symptoms decreased over time (Table II). Fever and dyspnoea were not frequently reported. At disease onset, rhinitis, headache and fatigue were most frequently observed. Gastro-intestinal symptoms were reported in a minority of the HCWs. At day 21, 43% still reported symptoms. Fatigue and anosmia or dysgeusia most frequently persisted at day 21. The majority (80.6%) of HCWs had a self-reported mild experience of COVID-19. No significant differences in symptomatology were found between repeat RT-PCR-positive and repeat RT-PCR-negative HCWs (data not shown).

### *Virology*

The median Ct-value of the initial RT-PCR was 21.1 (IQR 8.0). Sixty-one (84.7%) participants had a repeat RT-PCR performed upon return to work, with a median of 13 days (range 6-42) post symptom onset. Thirty (49.1%) of them were positive with a median Ct-value of 29.2 (IQR 3.0). Eleven participants did not have a repeat RT-PCR performed.

Twenty-two out of the 30 repeat RT-PCR-positive participants (73.3%) had a repeat RT-PCR specimen with a Ct-value <30 (corresponding with 36% of all HCW for which repeat RT-PCR results were available). Of these 22 participants, we identified eleven SARS-CoV2 RNA-positive within-department-contacts as potential secondary transmissions. Specimens of these eleven within-department-contacts were sequenced (Figure 1).

Phylogenetic analysis revealed one pair of identical viral genomes of return-to-work and corresponding within-department-contact and one pair that differed two single-nucleotide polymorphisms. Contact tracing and epidemiological data of these two pairs showed no indications of onward transmission. Eight return-to-work and corresponding within-department-contact pairs had pairwise genetic distances not compatible with direct transmission (minimal pairwise genetic distance of five single-nucleotide polymorphisms).

*Serology*

All HCWs of which serum was collected developed antibodies during the follow-up period (data not shown). Upon symptom resolution, antibodies were detected in 42 out of 48 (87.5%) HCWs of which serum was collected at this time point. At 16 weeks, antibodies were detected in 97.5% of the HCWs. Two HCWs seroreverted (from positive to negative antibody status) during the follow-up period, within 8 weeks after disease onset. No significant difference in presence of antibodies was found between repeat RT-PCR-positive and repeat RT-PCR-negative HCWs.

## DISCUSSION

HCWs are at increased risk for SARS-CoV-2 infection and onward transmission to colleagues and patients. Guidelines are inconsistent on the timing for SARS-CoV-2 positive HCWs to return to work. We studied symptoms, repeated RT-PCR, risk of transmission and antibody dynamics in HCWs when returning to work. We found a generally mild course of COVID-19 and despite high SARS-CoV-2 RNA viral loads, no evidence for transmission from returning HCWs upon resolution of symptoms was found.

Surprisingly, almost 50% of the repeat RT-PCR when returning to work were positive with Ct-values suggesting the possibility of replicating virus. Our study showed RT-PCR positivity up to 38 days after symptom onset, which is in line with the now well-established experience that RNA may be detected for longer periods after a SARS-CoV-2 infection.[9-11] The relatively high viral loads (Ct-values <30) found in 36% of the HCW upon return to work in our study raised the question whether our hospital guideline is stringent enough to prevent nosocomial transmission, especially since national and international guidelines generally recommend a longer duration of isolation after COVID-19 in HCWs.[4-7]

Ct-values were used as surrogate marker for infectivity in accordance with previous studies, as they correlate well with the ability to culture (viable) virus and a cut-off of 30 is associated with the inability to culture virus. [19,20] Viral sequencing was performed to investigate whether onward transmission occurred by HCW who returned to work. Phylogenetic analysis showed one pair of identical viral sequences of a return-to-work study participant and within-department-contact and one pair that differed two single-nucleotide polymorphisms. For the pair with identical sequences the probability of direct transmission was deemed negligible after assessment of the contact tracing data as the index HCW worked from home during one

month after his infection and there was no contact to other HCWs at that time. Epidemiological assessment of the pair differing two single-nucleotide polymorphisms suggested that direct transmission was unlikely, as the return-to-work HCW remained home for 14 days after onset of complaints, had no complaints when returning to work, and the HCWs did not know each other. Thus, despite the high numbers of positive specimens with theoretically viable virus in this study, we found no evidence for onward transmission at work from returning HCW upon resolution of symptoms. However, the possibility of HCW-to-HCW transmission cannot be completely ruled out as in this study onward transmission may have occurred but remained undiagnosed in asymptomatic individuals.

A possible explanation for the identical viral genomes found in one return-to-work and corresponding within-department-contact pair may be exposure to comparable genomes circulating in The Netherlands at that time (as evidenced by identical genomes detected in contemporaneous SARS-CoV-2 viral genomes from the Netherlands, Table A.I). Although direct transmission could not definitely be ruled out for one pair in this study, a symptom-based strategy for determining when HCWs with a SARS-CoV-2 infection could return to work as in the current hospital guidelines are considered adequate and safe. Nevertheless, as this study was performed before the emergence of the alpha-variant, the emergence of new circulating variants associated with higher transmissibility[21, 22] may require guideline re-evaluation. Moreover, as study participation was on a voluntary basis, the included HCW population may have behaved more compliant with social distancing rules and personal protection guidelines. This could partially explain the absence of documented transmission by HCW after returning to work. Infection prevention measures such as physical distancing, personal protective equipment and vaccination should remain a priority for SARS-CoV-2 in-hospital infection control, as there is evidence that HCW-to-HCW transmission is an

important route of nosocomial infections[22-25] and transmissions generally occur before a HCW tests positive.

Despite low symptomatology, all HCWs in this cohort seroconverted. Comparable prospective studies showed similar but somewhat lower rates, possibly due to a shorter follow up period[26, 27] or because only IgG was measured.[28] Further research is needed to determine long-term protection and protection against new variants. Presence of antibodies seemed not associated with repeat RT-PCR positivity, indicating that even mild infections with a faster viral clearance result in antibody response. The majority of the participants (87.5%) had already developed antibodies when returning to work, which further reduces the assumed risk of transmission at this time point given the negative correlation with SARS-CoV-2 specific antibodies and the presence of infectious virus.[14, 15]

The main limitation of our study is that infectivity of the HCWs when returning to work could not be determined. In addition, the small sample size of our study, especially the limited number of HCWs returning to work with high viral loads, may have influenced our conclusions about the risk of transmission. However, extensive phylogenetic as well as background analyses in combination with contact tracing data showed no evidence for direct transmission.

A strength of this study is that it was prospectively conducted in confirmed SARS-CoV-2 positive HCWs. Most studies in HCWs are retrospective seroprevalence studies in which it is impossible to accurately evaluate symptomatology or determine the antibody responses in this specific population. Furthermore, all analyses were performed in the same laboratory, making it possible to compare Ct-values amongst participants.

## Conclusions

To conclude, our study revealed relatively high viral loads in SARS-CoV-2 positive HCWs when returning to work after symptom resolution. As no evidence for secondary HCW-to-HCW transmission after returning to work was found, a symptom-based approach appears adequate in preventing SARS-CoV-2 infections from returning HCW. Since HCW-to-HCW transmission is a common source of nosocomial SARS-CoV-2 infections, infection prevention measures and guideline adherence should remain priorities when shaping future hospital policy and practice.

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## DECLARATIONS OF INTEREST

None.

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372 **TABLES**

373 **Table I. Descriptive statistics of the study cohort**

| Characteristic | Value |
|---|---|
| Age, median (IQR) | 33 (19.0) |
| Female, No. (%) | 54 (75.0) |
| Body mass index, median (IQR) | 23 (6.3) |
| Profession, No. (%) | |
| Direct patient contact | 44 (61.1) |
| Physician | 10 (15.3) |
| Nurse | 20 (27.8) |
| Medical intern | 8 (11.1) |
| Clinical assistant | 4 (5.6) |
| Other | 2 (2.8) |
| No direct patient contact | 28 (38.9) |
| Researcher | 10 (13.9) |
| Pharmacy staff/assistant | 5 (6.9) |
| Laboratory technician | 2 (2.8) |
| Other | 11 (15.3) |
| Comorbidities, No. (%) | |
| High blood pressure | 3 (4.2) |
| Diabetes | 1 (1.4) |
| Cardiovascular disease | 1 (1.4) |
| Asthma | 4 (5.6) |
| Other | 4 (5.6) |
| Continued to work while having symptoms, No. (%) | |
| Yes[a] | 15 (20.8) |
| No knowledge of regulations | 0 (0.0) |
| Mild symptoms | 12 (80.0) |
| Devoted symptoms to another cause | 7 (40.0) |
| Work pressure/sense of responsibility | 3 (20.0) |
| No | 48 (66.7) |
| Don't Know | 3 (4.2) |
| Unknown | 6 (8.3) |

[a] *Multiple answers were possible*

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**Table II. Detailed symptomatology in HCWs with RT-PCR confirmed COVID-19**

| Symptom | Time of interview | | | | |
|---|---|---|---|---|---|
| | **Disease onset (n=72)** | **Day 2 (n=72)** | **Day 7 (n=71)** | **Day 14 (n=71)** | **Day 21 (n=71)** |
| Respiratory symptoms | | | | | |
| Coughing | 22 (30.6) | 39 (54.9) | 27 (38.0) | 12 (16.9) | 9 (12.7) |
| Pharyngitis | 21 (29.2) | 19 (26.8) | 7 (9.9) | 6 (8.5) | 3 (4.2) |
| Dyspnoea | 7 (9.7) | 11 (15.5) | 11 (15.5) | 5 (7.0) | 9 (12.7) |
| Rhinitis | 30 (41.7) | 48 (67.6) | 29 (40.8) | 11 (15.5) | 8 (11.3) |
| Gastro intestinal symptoms | | | | | |
| Abdominal pain | 4 (5.6) | 7 (9.9) | 3 (4.2) | 2 (2.8) | 0 (0.0) |
| Diarrhoea | 7 (9.7) | 8 (11.1) | 2 (2.8) | 1 (1.4) | 1 (1.4) |
| Nausea | 3 (4.2) | 7 (9.9) | 2 (2.8) | 2 (2.8) | 3 (4.2) |
| Vomiting | 1 (1.4) | 3 (4.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Anorexia | 12 (16.7) | 26 (36.6) | 20 (28.2) | 5 (7.0) | 4 (5.6) |
| Other symptoms | | | | | |
| Fever | 13 (18.1) | 18 (25.4) | 4 (5.6) | 1 (1.4) | 0 (0.0) |
| Myalgia | 19 (26.4) | 23 (32.4) | 9 (12.7) | 3 (4.2) | 3 (4.2) |
| Headache | 37 (51.4) | 39 (54.9) | 16 (22.5) | 12 (16.9) | 9 (12.7) |
| Fatigue | 32 (44.4) | 49 (69.0) | 35 (49.3) | 22 (31.0) | 18 (25.4) |
| Anosmia or dysgeusia | 13 (18.9) | 25 (35.2) | 36 (50.7) | 22 (31.0) | 17 (23.9) |

| | | | | | |
|---|---|---|---|---|---|
| No symptoms experienced | 0 (0.0) | 0 (0.0) | 15 (21.1) | 36 (50.7) | 40 (56.3) |

*HCWs = healthcare workers; COVID-19 = coronavirus disease 2019*

## FIGURE LEGENDS

**Figure 1. Maximum likelihood phylogeny of SARS-CoV-2 sequences with identified potential transmission clusters.**

A condensed maximum-likelihood phylogeny of SARS-CoV-2 sequences that were collected (marked with tip shapes) and a random sample of contemporaneous reference sequences (no tips) circulating within the Netherlands. Tip shapes are coloured according to the wards the HCWs (circle and square tips) and their within-department-contacts (diamond tips) were working on. The Figure zooms in on two potential transmission clusters that were found.

**Table A.I. Contemporaneous SARS-CoV-2 viral genomes from the Netherlands, derived from the GISAID database**